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14. ABSTRACT We hypothesize that by enriching the diet with ω -3 PUFAs PCa tumor progression will be significantly reduced. Patients with localized PCa will be enrolled in a randomized, double-blinded phase-I clinical trial in which they will be given ω -3 fish oil or control oleic acid supplements 5 weeks prior to prostatectomy. We will evaluate differential protein and phosphopeptide expression in PCa cells, obtained from laser capture microdissected tissue, by mass spectrometry. As primary endpoints, we will compare proliferation and apoptosis in tumors from each group using immunohistochemistry and DNA nick end labeling. As secondary endpoints, we will compare serum prostate specific antigen and hormone levels. We will also measure levels of dietary PUFAs in red blood cell membranes as well as FASN and PUFA metabolic products in prostate tissue using high performance liquid chromatography, mass spectrometry, and gas chromatography.					
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Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	4-7
Synergy Statement.....	4
Key Research Accomplishments.....	4
Reportable Outcomes.....	5
Conclusion.....	5

Introduction

Currently, no curative therapy exists for advanced, metastatic prostate cancer (PCa). However, given the long latency period of PCa progression coupled with the close association between aging and disease incidence, therapies that impede cancer growth would make PCa clinically irrelevant. Dietary intervention represents one such therapy. Epidemiological studies demonstrate that intake of ω -3 polyunsaturated fatty acids (PUFAs) decreases PCa risk while ω -6 intake increases risk. Work from our laboratories and others suggests that the metabolites of dietary ω -3 and -6 PUFAs directly affect PCa and the ability to do so depends on intake and metabolic enzyme expression. Omega-3 and -6 PUFAs compete as substrates for cyclooxygenase-2 and 15-lipoxygenase-1, both elevated in PCa; these enzymes convert ω -3 PUFAs to anti-tumorigenic metabolites and ω -6 to pro-tumorigenic ones. PCa cells also have elevated fatty acid synthase (FASN). FASN regulates the expression of a myriad of genes, including the PUFA metabolic enzymes Δ -5 and -6 desaturase and phospholipases that liberate arachidonic acid, which together may affect the pool of PUFAs. In addition, ω -3 inhibits FASN, inducing apoptosis in PCa cell lines. These data provide evidence that ω -3 PUFAs, through anabolic and catabolic fatty acid pathways as well as possibly other pathways, modulate PCa. We hypothesize that by enriching the diet with ω -3 PUFAs PCa tumor progression will be significantly reduced. Patients with localized PCa will be enrolled in a randomized, double-blinded phase-I clinical trial in which they will be given ω -3 fish oil or control oleic acid supplements 5 weeks prior to prostatectomy. We will evaluate differential protein and phosphopeptide expression in PCa cells, obtained from laser capture microdissected tissue, by nanoflow reversed-phase liquid chromatography coupled online with high-resolution and – accuracy tandem mass spectrometry. As primary endpoints, we will compare proliferation and apoptosis in tumors from each group using immunohistochemistry and DNA nick end labeling. As secondary endpoints, we will compare serum prostate specific antigen and hormone levels. We will also measure levels of dietary PUFAs in red blood cell membranes as well as FASN and PUFA metabolic products in prostate tissue using high performance liquid chromatography, mass spectrometry, and gas chromatography.

Body

Because of technical difficulties associated with submission and resubmission of revised protocols, initiation of trial meeting delays the proposed recruitment of 50 men (25 men from each treatment arm) did not take place. However, we were able to get the protocol in place which had to be reapproved by the Department of Defense (DoD). We resubmitted the protocol as an amendment to the University of Pittsburgh institutional review board (IRB) which was approved. During the performance period, however, both of the collaborating PIs (Drs. Beth Pflug and Uddhav Kelavkar) notified of their intention to move to different institutions. Subsequent to this period of performance, the initiating PI, Dr Conrads, also moved to assume a new position in a capacity that no longer enables his participation in the grant.

Key Research Accomplishments

None to report.

Reportable Outcomes

None to report.

Conclusions

With the movement of the PIs for this grant to different institutions, progress in laying the regulatory ground work for this study has experienced considerable delays, which ultimately led to lack of progress in the initiation of the clinical trial and subsequent scientific and translational aims of the grant.